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(54) Title: NEW USE OF A PYRIDAZINONE DERIVATIVE

(57) Abstract

A method for the treatment of neurohumoral imbalance caused by alterations of cardiac function to prevent the development of heart failure or a method of increasing calcium sensitivity of contractile proteins of cardiac muscle comprises administering an effective amount of (R)–N–[4–(1,4,5,6–tetrahydro–6–oxo–3–pyridazinyl)phenyl]acetamide to a mammal in need of such treatment.

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# NEW USE OF A PYRIDAZINONE DERIVATIVE

The invention relates to a method of increasing calcium sensitivity of contractile proteins in the cardiac muscle and to a method for treating neurohumoral imbalance caused by alterations of cardiac function to prevent the development of heart failure, comprising administering an effective amount of (R)-N-[4-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)phenyl]acetamide.

Racemic N-[4-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)phenyl]acetamide (I) has been described earlier as a hypotensive agent (US 3,746,712) and as a cardiotonic agent having inotropic activity (US 4,397,854). It has been reported that the inotropic action of racemic N-[4-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)phenyl]acetamide is based on phosphodiesterase III (PDE III) enzyme inhibition (Ishimori t. et al., Arzneim.- Forsch. (1994), 44(5), 583-8). The compound (I) has an asymmetric carbon atom and may therefore exist in two stereoisomeric forms. The (R)- and (S)- enantiomers of (I) have been earlier described in Japanese patent application no. (Heisei) JP 3163050. However, biological activity data for the enantiomers has not been described.

At the moment series of inotropic compounds, e.g. milrinone, the mechanism of which is based on PDE III inhibition are in clinical trials for the treatment of heart failure. These compounds increase the contractility of the cardiac muscle by increasing the calcium current into the cardiac muscle and produce vasodilatation. The contraction in cardiac muscle is triggered by the binding of calcium to troponin in the thin filament of contractile proteins. However, it is possible that the long-term application of PDE III inhibitors leads to calcium overload in the cardiac muscle which can trigger arrhythmias. Therefore, the main mechanism to increase cardiac contractility should be a mechanism which does not produce calcium overload. The enhancement of the turnover of intracellular calcium released from sarcoplasmic reticulum and the increase of calcium sensitivity of contractile proteins are such mechanisms which do not induce calcium overload.

When a patient has harmful alterations in the cardiac function, the contractility of the cardiac muscle can still be maintained through neurohumoral activation in the body, which increases the intake of calcium in the cardiac muscle. In this situation the calcium overload can trigger arrhythmias, and prolonged neurohumoral activation will accelerate the development of heart failure. Neurohumoral imbalance can be indicated, for example, by altered renin and noradrenaline concentrations in a patient's plasma.

PDE III inhibitors can not be used chronically in the treatment of neurohumoral imbalance because they further increase the intake of calcium into the cardiac muscle. However, the use of a calcium sensitizer can sufficiently increase the contractility already in normal and decreased calcium concentrations which would reduce the need of neurohumoral activation and thereby prevent the development of heart failure.

It has been now discovered that the (R)-enantiomer of N-[4-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)phenyl]acetamide has a calcium sensitizing effect on the thin filament of contractile proteins and this is its main mechanism to increase cardiac contractility. This was unexpected since the mechanism of racemic compound (I) was reported to be PDE III inhibition. Thus, being a calcium sensitizer the (R)-enantiomer of N-[4-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)phenyl]acetamide has a utility in the treatment of neurohumoral imbalance caused by alterations of cardiac function to prevent the development of heart failure.

The present invention relates to a method for the treatment of neurohumoral imbalance caused by alterations of cardiac function to prevent the development of heart failure by administering, e.g. orally or parenterally in a solid or liquid dosage form, an effective amount of (R)-enantiomer of compound (I) to a patient in need of such treatment.

The present invention also relates to a method of increasing calcium sensitivity of contractile proteins by administering an effective amount of (R)-enantiomer of compound (I) to a patient in need of such treatment.

The present invention further relates to a use of (R)-enantiomer of compound (I) in the manufacture of a medicament for use in the treatment of neurohumoral imbalance caused by alterations of cardiac function to prevent the development of heart failure.

The present invention further relates to a use of (R)-enantiomer of compound (I) in the manufacture of a medicament for increasing calcium sensitivity of contractile proteins.

The pharmaceutically active compound according to this invention is formulated into dosage forms using the principles known in the art. It is given to a patient as such or in combination with suitable pharmaceutical excipients in the form of tablets, dragees, capsules, suppositories, emulsions, suspensions or solutions. The composition according to the invention contains a therapeutically effective amount of the pharmaceutically active compound of the invention. The content of the active compound is in the composition from about 0.5 to 100 % per weight.

In the claimed method the compound of the invention may be administered to man in oral doses ranging from about 0.1 to 500 mg, preferably 0,5 to 10 mg, per day. Choosing suitable ingredients for the composition is a routine for those of ordinary skill in the art. It is evident that suitable carriers, solvents, gel forming ingredients, dispersion forming ingredients, antioxidants, colours, sweeteners, wetting compounds and other ingredients normally used in this field of technology may be also used.

The following example will further illustrate the invention.

EXAMPLE 1. Preparation of (R)-N-[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]acetamide

(R)-6-(4-aminophenyl)-4,5-dihydro-5-methyl-3(2H)-pyridazinone (30,0 g) and acetonitrile (600 mL) were mixed and the mixture was refluxed until the starting material dissolves. Acetic anhydride (30,0 mL) was added to the refluxing mixture. After 10 min the solution was allowed to cool to room temperature. The product was filtered, washed with acetonitrile and dried. Yield 30,8 g, m.p. 230-232 °C, $^1$H-NMR (DMSO-$d_6$, 400MHz) 1.06 (d, 3H, J = 7.3 Hz), 2.06 (s, 3H), 2.22 (d, 1H, J = 16.6 Hz), 2,67 (dd, 1H, J = 16.6 Hz, 6.8 Hz), 3.35 (m, 1H), 7.63 (d, 2H, J = 8.8 Hz), 7.72 (d, 2H, J = 8.8 Hz), 10.09 (s,1H), 10.88 (s, 1H). $[\alpha]_D^{20}$ = -466° (c = 2 mg/ml, DMF).

The usefulness of the compound of the invention is demonstrated by the following experiments. Compound A is (R)-N-[4-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)phenyl]acetamide.

Calcium sensitizing effect in skinned cardiac fiber

Left ventricular papillary muscle of the guinea-pig was dissected and rinsed in ice-cold Tyrode solution. Thereafter the papillary muscle was immersed into a solution containing (mM): Potassium acetate 74.7, EGTA 10, $MgSO_4$ 5.4, ATP-$Na_2$ 4, DTE 1, MOPS 20, pH 7.0 (by 1 M KOH). Subsequently, the papillary muscle was sonicated at 10 Watt for 60 sec in this ice-cold solution. The distance between ultrasound probe and the papillary muscle was 10 mm. The fibers (< 200 µm in diameter) were dissected from surface of sonicated papillary muscles. Moreover, the sonicated and dissected fibers were kept for 30 min in a "skinning" solution (ice-cold) containing saponin (250 µg/ml) in addition to the other constituents. Continuous magnetic stirring was used during this treatment.

The fibers which were further dissected (< 100 µm in diameter) were then mounted horizontally with a glue (cellulose acetate in acetone) between a steel-rod extension of isometric force transducer (AME-801 strain gauge, Horten Electronics,

Norway) and a glass rod attached to a micro-manipulator. The force transducer was connected to an amplifier. The fibers were kept in the "relaxing" solution containing (mM): imidazole 30, ATP-$Na_2$ 10, $NaN_3$ 5, EGTA 5, $MgCl_2$ 12.5, and 350 U creatinkinase. The temperature of the solution was 22°C and the pH was set to 6.7 by 1 M KOH. The ionic strength was adjusted with 1 M KCl to correspond that of the "activating" solution. The composition of the "activating" solution was the same as that of the "relaxing" solution except that it contained also $CaCl_2$. The fibers were induced to contract in desired free pCas (-log[$Ca^{2+}$]) which were obtained by properly mixing of the "relaxing" and "activating" solutions. Tension produced by a fiber at pCa 4.8 was taken as maximum response. At the beginning of the experiment the fiber was stretched as described above.

The calcium sensitizing effects of Compound A and milrinone are shown in Table 1.

TABLE 1. Calcium sensitizing effect in skinned fiber at pCa 5.6

| | | Change in force / % of control |
|---|---|---|
| Compound A | 0.3 µM | + 26 ± 6 (n = 7) |
| | 3 µM | + 109 ± 35 (n = 7) |
| Milrinone | | Ineffective |

Positive inotropic effect in paced cardiac muscle

Four weeks old guinea-pigs weighing about 350 g were used. In the experiments the right ventricular papillary muscle of the heart was mounted for measurement of isometric tension in organ bath containing modified Tyrode solution (37°C) bubbled with 95 % $O_2$, 5 % $CO_2$. The composition of the modified Tyrode solution was (mM): NaCl 135; $MgCl_2 \cdot 6H_2O$ 1; KCl 5; $CaCl2 \cdot 2H_2O$ 2; $NaHCO_3$ 15; $Na_2HPO_4 \cdot 2H_2O$ 1; glucose 10; pH 7.3 - 7.4. The volume of the open horizontal chamber was 1 ml and flow rate of the superfusion solution running through the chamber was 5 ml/min. Papillary muscle (< 1 mm in diameter) was stretched horizontally between force-displacement transducer (FT 0.3 C) and a needle fixed to the bottom of the chamber. An initial stretching tension of 300 mg was applied to the muscle which was electrically

stimulated (Stimulator model SEC 48 F, Grass Instruments) via platinum field electrodes at 1 Hz with rectangular pulses (duration 4 ms). The stimulation occurred at twice threshold voltage in order to achieve simultaneous activation of all myocytes in the capillary muscle. A force-displacement transducer was connected to a polygraph D.C. driver amplifier (model 7 DA, Grass Instruments) and a programmable scanner (model SI 5010, Tetronix). The amplified signal was digitized with 1 kHz frequency by a programmable digitizer (model 390 A, Sony Tetronix).

The inotropic effects of Compound A and milrinone are shown in Table 2.

TABLE 2. Positive inotropic effect in guinea-pig papillary muscle

| | $EC_{50}$ / μM |
|---|---|
| Compound A | 0.1 |
| Milrinone | 2 |

CLAIMS

1. Use of (R)-N-[4-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)phenyl]acetamide in the manufacture of a medicament for use in the treatment of neurohumoral imbalance caused by alterations of cardiac function to prevent the development of heart failure.

2. Use of (R)-N-[4-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)phenyl]acetamide in the manufacture of a medicament for increasing calcium sensitivity of contractile proteins of cardiac muscle.

3. A method for the treatment of neurohumoral imbalance caused by alterations of cardiac function to prevent the development of heart failure by administering an effective amount of (R)-N-[4-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)phenyl]-acetamide to a mammal in need of such treatment.

4. A method of increasing calcium sensitivity of contractile proteins of cardiac muscle by administering an effective amount of (R)-N-[4-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)phenyl]acetamide to a patient in need of such treatment.

# INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/FI 99/00449

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 4 397 854 A (SIRCAR ILA)<br>9 August 1983 (1983-08-09)<br>column 3, line 38-41<br>column 4, line 32 -column 6, line 34;<br>claims 1-4<br>abstract | 1-4 |
| X | JP 58 008015 A (MITSUBISHI KASEI KOGYO KK)<br>18 January 1983 (1983-01-18)<br>the whole document | 1-4 |

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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# INTERNATIONAL SEARCH REPORT

Inter ›nal Application No
PCT/FI 99/00449

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | SEKI, TOSHIMI ET AL: "Studies on agents with vasodilator and.beta.-blocking activities. V. Synthesis and pharmacological activity of the optical isomers of TZC-5665" CHEM. PHARM. BULL. (1998), 46(1), 84-96 , XP002119278 figure 2 --- | 1-4 |
| X | ROBERTSON, DAVID W. ET AL: "Imidazole-pyridine bioisosterism: comparison of the inotropic activities of pyridine- and imidazole-substituted 6-phenyldihydropyridazinone cardiotonics" J. MED. CHEM. (1988), 31(2), 461-5 , XP002119279 abstract; figure 1; table 1 page 463, column 1, paragraph 2 -page 464, column 1, paragraph 3 --- | 1-4 |
| X | ROBERTSON, DAVID W. ET AL: "Dihydropyridazinone cardiotonics. The discovery and inotropic activity of 1,3-dihydro-3,3-dimethyl-5-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)-2H-indol-2-one" J. MED. CHEM. (1986), 29(10), 1832-40 , XP002119280 page 1833, column 2, paragraph 2 -page 1834, column 1, paragraph 2; figure 1; tables 2,3 page 1838, column 1, paragraph 2 --- | 1-4 |
| X | MOHAN, C. G. ET AL: "Electric field mapping and structure-activity relationships for some dihydropyridazinone cardiotonics" THEOCHEM (1995), 332(1-2), 171-6 , XP002119281 abstract; figures 1,4; table 1 --- | 1-4 |
| X | COATES, WILLIAM J. ET AL: "1,4-Bis(3-oxo-2,3-dihydropyridazin-6-yl)benzene analogs: potent phosphodiesterase inhibitors and inodilators" J. MED. CHEM. (1990), 33(6), 1735-41 , XP002119282 see scheme 2 abstract; table 1 --- -/-- | 1-4 |

# INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/FI 99/00449

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | SIRCAR, I. ET AL: "Cardiotonic agents. 10. Cardiovascular evaluation of dihydropyridazinone ring-opened analogs of imazodan" EUR. J. MED. CHEM. (1989), 24(4), 349-55 , XP002119283 abstract; tables 3,4 --- | 1-4 |
| X | BAKEWELL, S. J. ET AL: "Inotropic, vasodilator and low Km, cAMP-selective, cGMP-inhibited phosphodiesterase (PDE III) inhibitory activities of 4a-methyl-4,4a-dihydro-5H-indeno'1,2-c!pyridazin-3(2H)-ones and 4a-methyl-4,4a,5,6-tetrahydrobenzo'h!cinnolin-3(2H)-ones" EUR. J. MED. CHEM. (1990), 25(9), 765-74 , XP002119284 abstract; table 1 page 770, column 1, paragraph 2 ----- | 1-4 |

# INTERNATIONAL SEARCH REPORT

I. national application No.
PCT/FI 99/00449

**B x I Observations wh re certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION SHEET PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Regarding Claims 1-4:
N-'4-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)phenyl!acetamide has no asymetric carbon atom or optical isomers and therefor the (R) or (S) isomers of this compound do not exist.
N-'4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl!acetamide as of example 1 exists as (R) and (S) isomers, the asymetric carbon being carbon numbered 4 in the pyridazinone ring.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No
PCT/FI 99/00449

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| US 4397854 A | 09-08-1983 | US 4404203 A | 13-09-1983 |
| JP 58008015 A | 18-01-1983 | NONE | |